

## Hypertrophic cardiomyopathy in Friedreich's ataxia

L. G. Van der Hauwaert and M. Dumoulin

*From the Department of Paediatrics, Section of Paediatric Cardiology, and the Hartcentrum, University Hospital Gasthuisberg, 3000 Leuven, Belgium*

*The cardiac findings in two sibs with Friedreich's ataxia are described. The clinical signs were suggestive of hypertrophic obstructive cardiomyopathy. During left heart catheterization a systolic pressure gradient across the left ventricular outflow tract could be provoked by an infusion of isoprenaline. Left ventricular angiocardiograms and echocardiograms showed gross thickening of the interventricular septum. In one patient a systolic anterior movement of the anterior leaflet of the mitral valve was seen. The importance of serial echocardiographic examination for patients with Friedreich's ataxia is emphasized.*

The association of myocardial disease with the neurological signs of progressive ataxia has been known for many years. In his original publication Friedreich (1863) mentioned 'severe fatty degeneration of the musculature of the left ventricle' in his necropsy report on 3 patients. That this association is almost invariable is shown by the pathological findings in 16 cases reported by Hewer (1969). All hearts examined were abnormal and showed muscle fibre hypertrophy and interstitial fibrosis. The high incidence of cardiac involvement in postmortem series may be explained by the fact that the vast majority of patients with Friedreich's ataxia die from cardiac complications, mainly intractable cardiac failure or rhythm disturbances, rather than from their neurological disorder. In clinical series electrocardiographic changes are usually described as the first sign of cardiac involvement, often several years before the development of cardiomegaly and heart failure.

Little attention has been paid to the haemodynamic findings in this rare and ill-understood neurocardiac syndrome. Right heart catheterization usually does not show any significant abnormality. Recent reports (Soulié *et al.*, 1965; Boehm, Dickerson, and Glasser, 1970; Gach, Andriange, and Franck, 1971) on left heart catheterization and angiocardiography have indicated that there is a striking similarity between the findings in the cardiomyopathy of Friedreich's ataxia and in hypertrophic obstructive cardiomyopathy (idiopathic

hypertrophic subaortic stenosis). In this report, we describe two sibs with Friedreich's ataxia in whom the clinical, haemodynamic, and echocardiographic findings of hypertrophic cardiomyopathy were present.

### Observations

#### Case 1

This boy, born 14 December 1955, was first evaluated at the age of 14 years because of a heart murmur, discovered at routine examination. When he was 7 years old the parents had first noticed that he had an unsteady gait and slurring of his speech. A few months before the examination he had to give up his training in a technical school because of progressive staggering and clumsiness. He tired easily on exertion. He has three brothers, one of whom (Case 2) presented with similar neurological symptoms. One of his two sisters suffers from epileptic attacks but is otherwise normal. One of his mother's first cousins died at the age of 30 years, allegedly from 'muscle weakness'.

On physical examination he was a thin boy with moderate kyphoscoliosis and generalized muscular dystrophy. Neurological examination showed the following abnormalities: slurring of speech, normal cranial nerves, ataxic gait, positive Romberg's sign, diminished muscle strength of the flexors of the legs and plantar flexors of the feet, weak tendon reflexes, particularly in the arms, normal superficial sensation, impaired vibration sense in the knees and iliac crests, and poor performance of finger pursuit

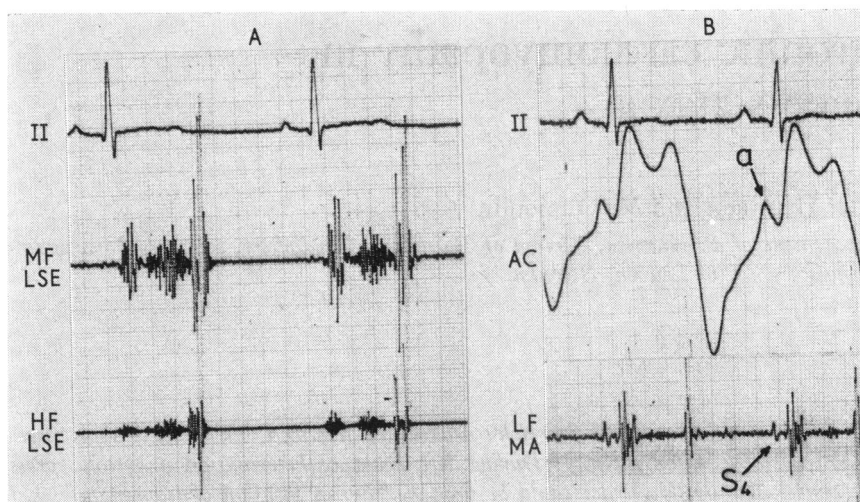


FIG. 1 Phonocardiogram from Case 1. (A) Lead II of electrocardiogram, medium-frequency (MF) and high-frequency (HF) recording from left sternal edge (LSE). Note that the ejection murmur reaches its maximum intensity relatively late, well beyond the middle of systole (defined as the interval from the first sound to the aortic component of the second sound). (B) Lead II of electrocardiogram, apex cardiogram (AC), and low-frequency phonocardiogram (LF) from mitral area (MA). An intense fourth sound ( $S_4$ ) coincides with a prominent a wave on the apexcardiogram. Both phenomena suggest decreased left ventricular compliance.

and heel-to-knee tests. There was no pes excavatus deformity. The arterial pulse was forceful and regular. Blood pressure was 120/70 mmHg. A heaving left ventricular impulse was felt 1 cm outside the midclavicular line. Jugular venous pressure was normal. A grade 3/6 midsystolic murmur was heard at the lower left sternal border and the apex. Splitting of the second sound was normal.

The phonocardiographic pattern of the murmur (Fig. 1) was diamond-shaped with its maximum intensity just before the middle of systole (defined as the interval from the first sound to the aortic component of the second sound). A loud atrial sound at the apex coincided with a prominent a wave on the apex cardiogram. A third sound was also recorded. The shape of the external carotid tracing was normal and did not show a pseudo-incisura. After the inhalation of amyl nitrite the intensity of the systolic murmur increased conspicuously. The downstroke on the carotid tracing became abrupt and the incisura less distinct.

The electrocardiogram (Fig. 2) showed regular sinus rhythm, a mean QRS axis of  $+70^\circ$ , a prominent P wave (3 mm) in II, and tall R waves in V5 (30 mm) and V6 (24 mm). Sharply inverted T waves were seen in II, III, aVF, V4, V5, and V6. The chest x-ray film was within normal limits.

Cardiac catheterization (Table) under local

anaesthesia showed normal systolic pressures and no gradient across the right ventricular outflow tract. The end-diastolic pressure in the right ventricle was slightly raised (8 mmHg). Arterial catheterization from the right brachial artery showed no pressure gradient between the left ventricle and the aorta. After an intravenous infusion of a small dose of isoprenaline ( $2\mu\text{g}/\text{min}$  for 3 minutes) the pressure in the left ventricle rose to 180/25 mmHg with a gradient of 70 mmHg on withdrawal to the ascending aorta.

Left ventricular biplane angiocardiograms (Fig. 3) showed several features characteristic of hypertrophic obstructive cardiomyopathy. The frontal view showed a small slit-like ventricular cavity in the end-systolic phase, a grossly thickened ventricular wall, and some indentation of its left upper portion in diastole. In the lateral systolic view a sharp angulation between the apex and the outflow tract was seen. The latter was narrowed by bulging of the hypertrophied interventricular septum opposite the anterior leaflet of the mitral valve. In diastole the narrowed subvalvar zone appeared as an inverted cone. There was no mitral regurgitation. The coronary arteries were large and dilated.

The echocardiogram<sup>1</sup> (Fig. 4) showed gross

<sup>1</sup>Echocardiograph with multiscan and M-mode scan facilities and Honeywell no. 1856 strip chart recorder.

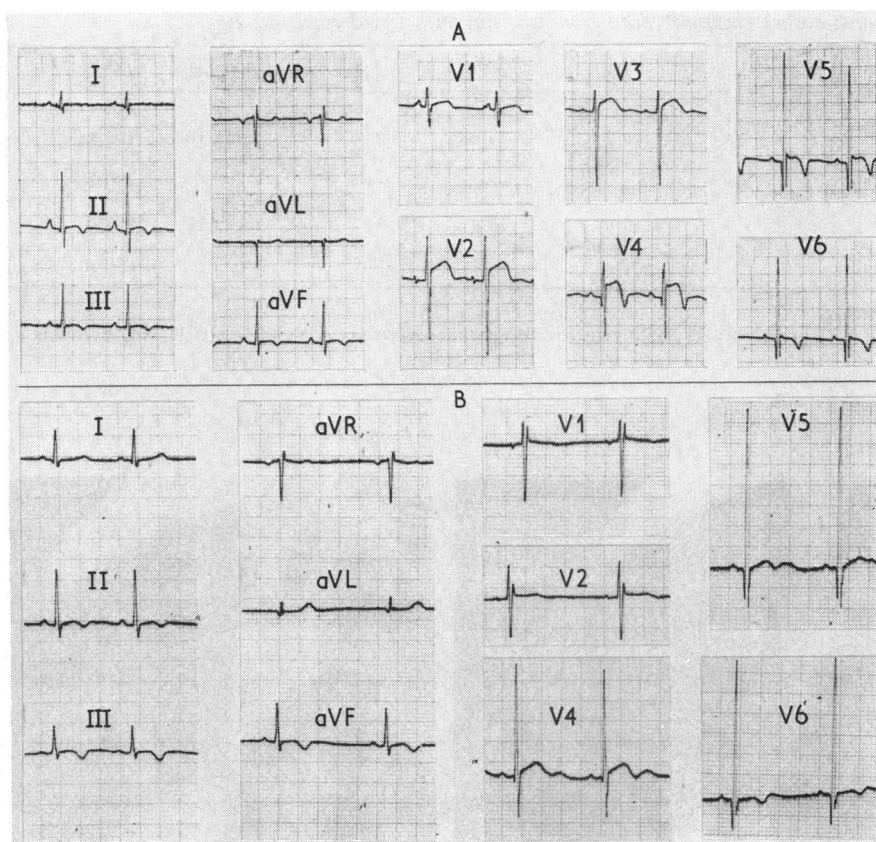


FIG. 2 Electrocardiogram from two sibs with Friedreich's ataxia. (A) Case 1, (B) Case 2. The records both show left ventricular hypertrophy and pronounced ST segment changes, and are very similar.

thickening of the interventricular septum (32 mm in end-diastole, 36 mm in systole) and the posterior left ventricular wall (22 mm). The septal posterior left ventricular wall ratio was 1.4:1. The transverse dimension of the left ventricular cavity, measured in the plane of maximal excursion of the mitral valve, was reduced (26 mm in end-diastole). Prominent systolic anterior movement (SAM) of the anterior leaflet of the mitral valve was recorded. Amyl nitrite inhalation enhanced the abnormal valve motion and produced almost complete occlusion of the outflow tract (Fig. 5).

#### Case 2

This boy, brother of the previous patient, was born 11 October 1960. Symptoms of mild ataxia first appeared at the age of 12. Fatigue on exertion was his only complaint. When he was first examined at 13 years of age his appearance, asthenic body build,

kypheoscoliosis, and unsteady gait gave him a striking resemblance to his older brother. Neurological examination showed the following: intermittent nystagmus, positive Romberg's sign, co-ordination only slightly impaired, hypotonia in upper and lower limbs, tendon reflexes much diminished in the arms but present in the legs, abdominal and cremasteric reflexes hyperactive, and normal superficial sensation and vibration sense. There was no pes cavus. On the whole the neurological disturbances were similar to those observed in his brother but seemed less severe. A grade 3/6 midsystolic murmur, preceded by an ejection sound, was best heard at the lower left sternal edge and the apex. It became much louder after the inhalation of amyl nitrite. The blood pressure was 120/65 mmHg.

The electrocardiogram (Fig. 2) showed considerable left ventricular hypertrophy in the

TABLE Cardiac catheterization\* data from two sibs with *Friedreich's ataxia*

	RA	RV	PA	PA wedge	LV	Ao
Case 1						
At rest	a 7 mean 4	24/8	24/12	mean 10	105/16	105/70
After isoprenaline	—	—	—	—	180/20	110/65
Case 2						
At rest	a 6 mean 4	18/4	14/7	mean 11	110/10	100/65
After isoprenaline	—	—	—	—	135/10	100/52

\*Pressures in mmHg.

Abbreviations: RA, right atrium; RV, right ventricle; PA, pulmonary artery; LV, left ventricle; Ao, ascending aorta.

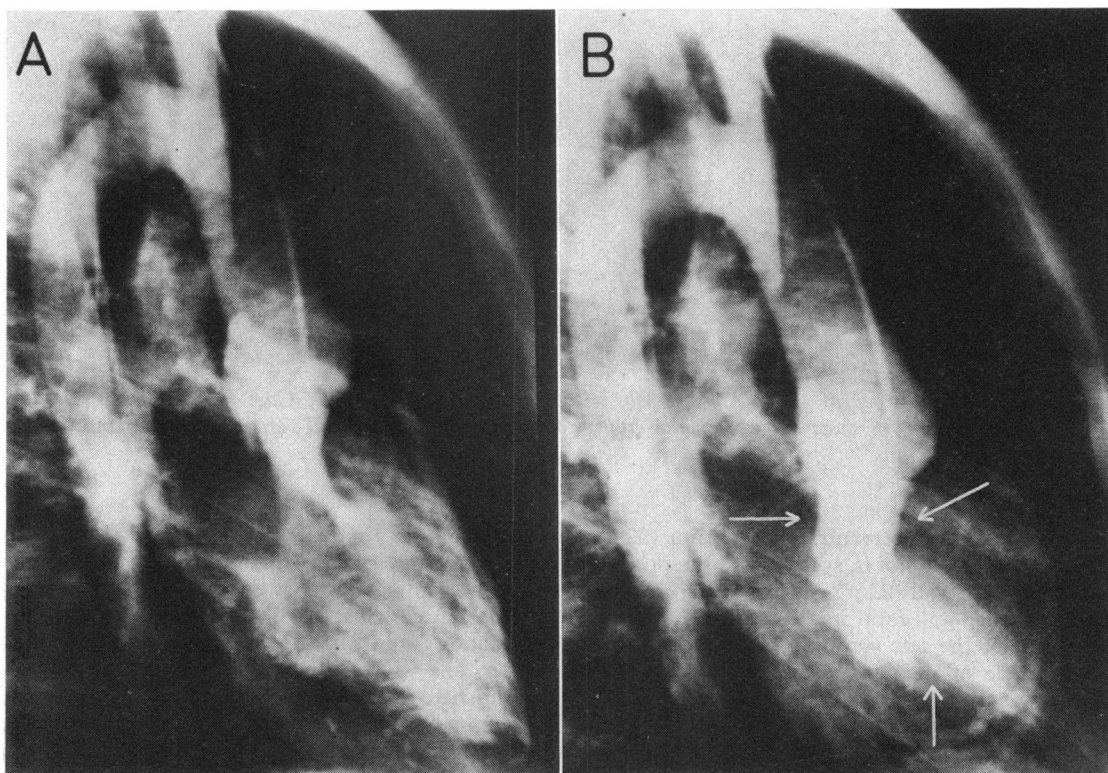


FIG. 3 Lateral view of left ventricular angiogram in Case 1. In diastole (A) the left ventricular outflow tract fails to open completely and has the appearance of an inverted cone beneath the aortic valve. Irregular translucent areas are produced by masses of hypertrophied myocardium. In systole (B) an angulation is seen between the body and the outflow tract. The latter is narrowed by bulging of the hypertrophied interventricular septum (oblique arrow) opposite the anterior leaflet of the mitral valve (horizontal arrow). Note the indentation produced by the hypertrophied posterior papillary muscle (vertical arrow). There is no mitral regurgitation.

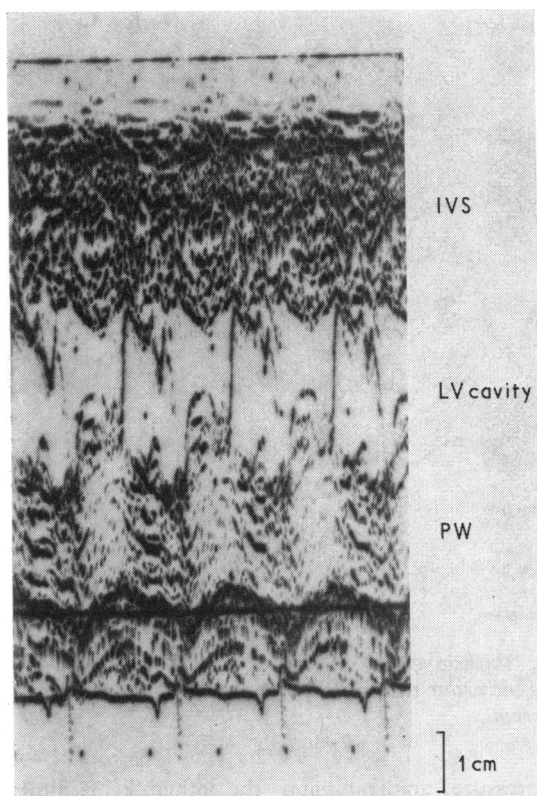


FIG. 4 Echocardiogram obtained in Case 1. Gross thickening of the interventricular septum (IVS) is seen. The dimension of the left ventricular (LV) cavity is reduced. The irregular echo of the endocardial surface of the left ventricular posterior wall (PW) is probably partly produced by abnormally positioned papillary muscles. Note the systolic anterior movement of the mitral valve which further reduces the ventricular cavity.

←

praecordial leads (32 mm R in V6). The T wave was slightly inverted in II, III, aVF, and the left praecordial leads. The chest x-ray was unremarkable.

At right heart catheterization (Table) normal pressures and oxygen saturations were found. Left heart catheterization from the right brachial artery showed no systolic gradient across the left ventricular outflow tract. During an infusion of isoprenaline ( $2\mu\text{g}/\text{min}$ ) the left ventricular systolic pressure quickly rose from 110 to 135 mmHg while the aortic systolic pressure was unchanged (100 mmHg). Left ventricular cineangiograms showed the same characteristics as in Case 1: very small end-systolic volume, thick ventricular wall, sharp angulation between the body of the left ventricle and its outflow tract, subvalvar narrowing

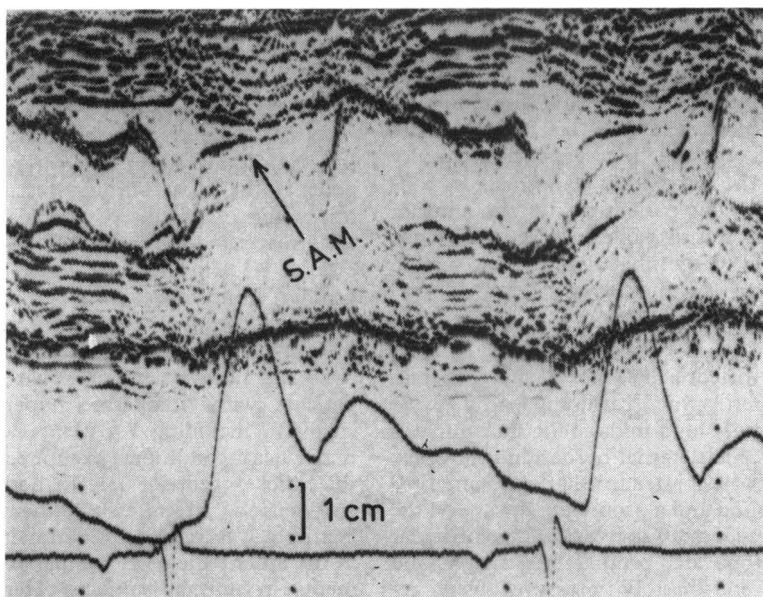


FIG. 5 Detail of left ventricular echocardiogram in Case 1, after inhalation of amyl nitrite. The systolic anterior movement of the mitral valve (SAM) is greatly enhanced so that the anterior leaflet and the septum are in close apposition. Sweep speed is 50 mm/s.



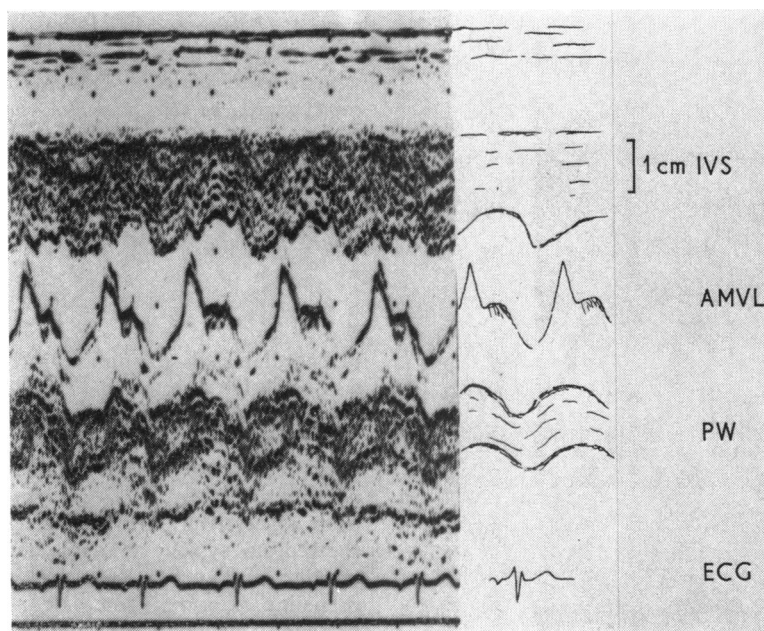


FIG. 6 Echocardiogram from Case 2 showing thickening of the interventricular septum (IVS) in the presence of a normal posterior left ventricular wall (PW). The movement of the anterior leaflet of the mitral valve (AMVL) is normal.

produced by septal hypertrophy, and the displaced anterior leaflet of the mitral valve.

The echocardiogram (Fig. 6) showed a thickened interventricular septum (17 mm in end-diastole and 23 mm in systole) with a normal posterior left ventricular wall (10 mm). The septal/posterior left ventricular wall ratio was thus 1.7:1. The transverse dimension of the left ventricular cavity (36 mm) was at the lower limit of normal. In contrast with the previous patient no systolic anterior movement of the mitral valve was observed, nor could it be provoked by inhalation of amyl nitrite.

### Discussion

In 2 sibs with Friedreich's ataxia signs characteristic of hypertrophic cardiomyopathy were found. A moderately loud midsystolic murmur was heard at the lower left sternal border and the apex. Its intensity increased after inhalation of amyl nitrite. An atrial sound and a prominent *a* wave on the apex cardiogram suggested decreased left ventricular compliance. In the older brother raised right and left ventricular end-diastolic pressures were recorded. At rest there were no gradients across the ventricular outflow tracts. During isoprenaline infusion, however, one patient developed a 70 mmHg

pressure gradient, and the other a 35 mmHg gradient between the left ventricle and the aorta. Left ventricular angiocardiograms showed the radiological changes usually seen in hypertrophic obstructive cardiomyopathy (Cohen *et al.*, 1964; Simon, Ross, and Gault, 1967).

As far as we know, echocardiographic studies in this condition have not been published. In both patients the most striking feature was the gross thickening of the interventricular septum with an abnormal septal/posterior left ventricular free wall ratio of 1.4:1 in the older and 1.7:1 in the younger brother. In normal subjects, in fixed left ventricular outflow obstruction, and in miscellaneous heart diseases, Henry, Clark, and Epstein (1973a) found that this ratio was approximately 1:1. In all 15 patients with 'idiopathic hypertrophic subaortic stenosis', including 7 patients without a gradient under basal conditions, examined by these authors, the ratio exceeded 1.3:1. In both our patients the end-diastolic transverse dimension of the left ventricle was reduced (26 mm in one and 36 mm in the other patient) as compared with the measurements in normal subjects (Henry *et al.*, 1975). Finally, in the older patient, who was more severely affected, a characteristic systolic anterior movement of the anterior mitral valve leaflet, as described in

hypertrophic obstructive cardiomyopathy (Shah, Gramiak, and Kramer, 1969; Pridie and Oakley, 1969) and in asymmetrical septal hypertrophy (Henry *et al.*, 1973a, 1975) was seen. The amplitude and duration of this abnormal valve movement could be greatly enhanced by the inhalation of amyl nitrite (Fig. 5). In the other patient no such valve movement could be recorded under basal conditions, nor could it be provoked.

Obviously the obstructive character of the cardiomyopathy in Friedreich's ataxia may easily be missed if not specifically looked for. Thorén (1964), who reported the results of right heart catheterization in 17 patients, mentioned raised end-diastolic pressures and a prominent *a* wave in the most advanced cases. Though he found no significant gradients across the infundibulum (left heart catheterization and pharmacological tests were not performed), he commented on the gross right ventricular hypertrophy and systolic narrowing of the infundibulum. This made him speculate that 'there is reason to compare this myocardial disease with the co-called stenosing and isolated myocardial hypertrophy'. Soulié *et al.* (1965) were probably the first to observe outflow tract obstruction in patients with Friedreich's ataxia. In 1 of the 4 patients who underwent cardiac catheterization, a gradient in both the right and left ventricular outflow tracts was found. In one patient Moore and Lambert (1968) found normal pressures under basal conditions but were able to provoke gradients in both outflow tracts by an infusion of isoprenaline. A similar observation was reported by Boehm *et al.* (1970) and by Gach *et al.* (1971). In the latter study the diagnosis of obstructive hypertrophic cardiomyopathy was confirmed by right and left ventricular angiocardiograms. They showed dynamic infundibular narrowing in the right ventricle and a funnel-shaped subvalvar stenosis in the left ventricle, produced by encroachment of a thick interventricular septum and an anteriorly displaced anterior leaflet of the mitral valve. A slight degree of mitral regurgitation was noted.

That outflow tract obstruction is not invariably associated with Friedreich's cardiomyopathy is borne out by the report of Ruschhaupt, Thilenius, and Cassels (1972). Having observed one child with severe hypertrophic subaortic stenosis, they undertook a haemodynamic study in 5 other children with Friedreich's ataxia. Right and left heart pressures were normal in all patients. Only in one patient could a 40 mmHg pressure gradient across the left ventricular outflow tract be induced by an infusion of isoprenaline.

It is very unlikely that the occasional occurrence of outflow tract obstruction in Friedreich's ataxia is

related to any specific metabolic or neurogenic disturbance in this condition. Obstructive cardiomyopathy has indeed been described in the course of various disorders which, as far as we know, have no common aetiological basis. Sporadic examples have been reported in association with glycogen storage disease (Ehlers *et al.*, 1962), lentiginosis (Somerville and Bonham-Carter, 1972), Noonan's syndrome (Ehlers *et al.*, 1972), and Refsum's disease (Pernot, Tridon, and Henry, 1973). From these cases and from a number of reports on cardiomyopathy in Friedreich's ataxia, including our own observations, it appears that the haemodynamic and angiocardigraphic features are indistinguishable from those seen in isolated hypertrophic obstructive cardiomyopathy, whether familial or sporadic. One is entitled, therefore, to consider the obstructive 'reaction' as non-specific. It probably reflects the severity of the myocardial hypertrophy, whatever the cause, and particularly its distribution within the myocardium. It is generally agreed that major involvement of the interventricular septum produces asymmetrical hypertrophy and therefore tends to cause left ventricular outflow obstruction (Goodwin and Oakley, 1972; Henry, Clark, and Epstein, 1973b) whereas thickening of the free wall of the left ventricle would lead to non-obstructive hypertrophic cardiomyopathy. In the present study and on previously published left ventricular angiocardiograms (Gach *et al.*, 1971), hypertrophy of the interventricular septum seemed to be a striking feature. Furthermore, the echocardiograms in our patients showed the characteristic abnormalities of asymmetrical septal hypertrophy (Henry *et al.*, 1973a). In the older patient, in whom the disease was more advanced, echocardiographic evidence of left ventricular outflow obstruction at rest was found.

One may speculate that our patients represent two stages of a slowly progressive form of hypertrophic cardiomyopathy characterized by asymmetrical septal hypertrophy and a variable degree of left ventricular outflow obstruction. More follow-up studies in a larger number of patients with Friedreich's ataxia are needed to corroborate this view. Because it is noninvasive, echocardiography seems to be the method of choice for these future studies.

We are grateful to Dr. B. Denef for his help with the recording and interpretation of the echocardiograms.

## References

- Boehm, T. M., Dickerson, R. B., and Glasser, S. P. (1970). Hypertrophic subaortic stenosis occurring in a patient with Friedreich's ataxia. *American Journal of the Medical Sciences*, **260**, 279.

- Cohen, J., Effat, H., Goodwin, J. F., Oakley, C. M., and Steiner, R. E. (1964). Hypertrophic obstructive cardiomyopathy. *British Heart Journal*, **26**, 16.
- Ehlers, K. H., Engle, M. A., Levin, A. R., and Deely, W. J. (1972). Eccentric ventricular hypertrophy in familial and sporadic instances of 46XX, XY Turner phenotype. *Circulation*, **45**, 639.
- Ehlers, K. H., Hagstrom, J. W. C., Lukas, D. S., Redo, S. F., and Engle, M. A. (1962). Glycogen-storage disease of the myocardium with obstruction to left ventricular outflow. *Circulation*, **25**, 96.
- Friedreich, N. (1863). Ueber degenerative atrophie der spinalen Hinterstränge. *Virchows Archiv für pathologische Anatomie und Physiologie*, **26**, 391 and 433; **27**, 1.
- Gach, J. V., Andriange, M., and Franck, G. (1971). Hypertrophic obstructive cardiomyopathy and Friedreich's ataxia. *American Journal of Cardiology*, **27**, 436.
- Goodwin, J. F., and Oakley, C. M. (1972). The cardiomyopathies. *British Heart Journal*, **34**, 545.
- Henry, W. L., Clark, C. E., and Epstein, S. E. (1973a). Asymmetric septal hypertrophy: echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation*, **47**, 225.
- Henry, W. L., Clark, C. E., and Epstein, S. E. (1973b). Asymmetric septal hypertrophy (ASH): the unifying link in the IHSS disease spectrum. *Circulation*, **47**, 827.
- Henry, W. L., Clark, C. E., Griffith, J. M., and Epstein, S. E. (1975). Mechanism of left ventricular outflow obstruction in patients with obstructive asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis). *American Journal of Cardiology*, **35**, 337.
- Hewer, R. L. (1969). The heart in Friedreich's ataxia. *British Heart Journal*, **31**, 5.
- Moore, A. A. D., and Lambert, E. D. (1968). Cardiomyopathy associated with muscular and neuromuscular disease. In *Paediatric Cardiology*, p. 766. Ed. by H. Watson. Lloyd-Luke, London.
- Pernot, C., Tridon, P., and Henry, M. (1973). Coeur et ataxies héréditaires. *Médecine Infantile*, **80**, 67.
- Pridie, R. B., and Oakley, C. M. (1969). Mitral valve movement in hypertrophic obstructive cardiomyopathy (abstract). *British Heart Journal*, **31**, 390.
- Ruschhaupt, D. G., Thilenius, O. G., and Cassels, D. E. (1972). Friedreich's ataxia associated with idiopathic hypertrophic subaortic stenosis. *American Heart Journal*, **84**, 95.
- Shah, P. M., Gramiak, R., and Kramer, D. H. (1969). Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. *Circulation*, **40**, 3.
- Simon, A. L., Ross, J., Jr., and Gault, J. H. (1967). Angiographic anatomy of the left ventricle and mitral valve in idiopathic hypertrophic subaortic stenosis. *Circulation*, **36**, 852.
- Somerville, J., and Bonham-Carter, R. E. (1972). The heart in lentiginosis. *British Heart Journal*, **34**, 58.
- Soulié, P., Vernant, P., Colonna, D., and Grynberg, J. C. (1965). Aspects cardiaques de la maladie de Friedreich. *Coeur et Médecine Interne*, **4**, 311.
- Thorén, C. (1964). Cardiomyopathy in Friedreich's ataxia. *Acta Paediatrica*, Suppl. 153.

Requests for reprints to Dr. L. G. Van der Hauwaert, Department of Paediatrics, University Hospital Gasthuisberg, 3000 Leuven, Belgium.